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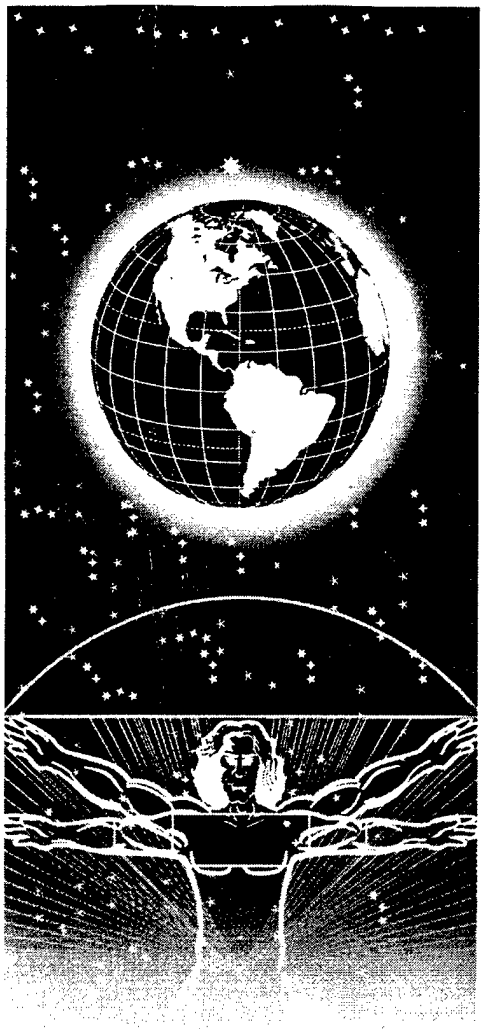

UNITED STATES AIR FORCE ARMSTRONG LABORATORY

Inhalation Uptake and Metabolism of Iodohalogenated Compounds, CF_3I, $C_6F_{13}I$, and C_3F_7I

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The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals* prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, National Academy Press, 1996, and the Animal Welfare Act of 1966, as amended.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

Terry A. Childress

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The purpose of this study was to measure the tissue to air partition coefficients and to describe the uptake and distribution kinetics of iodohalogenated compounds iodotrifluoromethane (CF_3I), perfluorohexyl iodide ($C_6F_{13}I$) and 1-iodoheptafluoropropane (C_3F_7I) via closed chamber recirculating gas uptake methods.

Inhalation pharmacokinetics for all chemicals were determined experimentally in Fischer-344 (F-344) male rats. A physiologically based pharmacokinetic (PBPK) model was used to describe mathematically the disposition and metabolism of the chemicals employing chemical-specific parameters and apparent whole-body metabolic constants calculated from these experiments.

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PREFACE

The research reported herein was conducted by the Toxic Hazards Research Unit, Man Tech Environmental Technology Inc., and serves as a technical report for the determination of the gas uptake kinetic of - iodotrifluoromethane (CF_3I), perfluorohexyl iodide ($C_6F_{13}I$), and 1-Iodoheptafluoropropane (C_3F_7I). The research described in this report began in June 1993 and was completed in Mar 1995.

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ABBREVIATIONS

°C	Degrees Celsius
F-344	Fischer 344 (rats)
FID	Flame ionization detector
g	Gram
GC	Gas chromatograph(y)
h	Hour
hrs	Hours
t	Time
L	Liter
m	Meter
min	Minute
mL	Milliliter
ppm	Parts per million
BW	Body weight
mm	Millimeter
PBPK	Physiological Based Pharmacokinetic
CF_3I	Iodotrifluoromethane
$C_6F_{13}I$	Perfluorohexyl Iodide
C_3F_7I	1-Iodoheptafluoropropane

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SECTION 1
INTRODUCTION

The purpose of this study was to measure the tissue to air partition coefficients and to describe the uptake and distribution kinetics of iodohalogenated compounds iodotrifluoromethane (CF_3I), perfluorohexyl iodide ($C_6F_{13}I$), and 1-iodoheptafluoropropane (C_3F_7I) via closed chamber recirculating gas uptake methods.

Inhalation pharmacokinetics for all chemicals were determined experimentally in Fischer-344 (F-344) male rats. A physiologically based pharmacokinetic (PBPK) model was used to describe mathematically the disposition and metabolism of the chemicals employing chemical-specific parameters and apparent whole-body metabolic constants calculated from these experiments

SECTION 2
METHODS/MATERIALS

Test Materials

Iodotrifluoromethane (CF_3I):

Manufacturer	PCR Inc. (Gainesville, FL)
Trade Name	Trifluoromethyl Iodide
CAS #	2314-97-8
Mol. Weight	195.9 g
Empirical Formula	CF_3I
Boiling Point (°C)	-22.5

Perfluorohexyl Iodide ($C_6F_{13}I$):

Manufacturer	Aldrich Chemical Co., Inc.(Milwaukee, WI)
Trade Name	Perfluorohexyl Iodide
CAS #	355-43-1
Mol. Weight	445.95 g
Empirical Formula	CF_3-CF_2-CF_2-CF_2-CF_2-CF_2I
Boiling Point (°C)	117

1-Iodoheptafluoropropane (C_3F_7I):

Manufacturer	Flura Corporation, Newport, TN
CAS #	754-34-7
Mol. Weight	295.93g
Empirical Formula	CF_3-CF_2-CF_2I
Boiling Point (°C)	40

Animals

Male Fischer 344 (F-344) (200 to 350 g) rats (*Rattus norvegicus*) were obtained from Charles River Breeding Laboratories (Kingston, NY). Animals received Purina Formulab #5008 and softened water *ad libitum*. They were housed in plastic cages (2-3/cage) with hardwood chip bedding prior to exposure and were maintained on a 12-hr light/ 12-hr dark light cycle at constant temperature (22 +/- 1°C) and humidity (40-60%). Cages were changed twice per week. Animals were marked for identification with a tail tattoo.

The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council, DHHS. National Institute of Health Publication #86-23, 1985, and the Animal Welfare Act of 1966, as amended.

Partition Coefficients

Partition coefficients were determined by using a modified version of the vial-equilibration technique described by Gargas *et al.* (1989). Whole tissue was harvested and minced into a tissue slurry versus prepared as a tissue homogenate in saline. Rats used to determine partition coefficients were sacrificed with CO_2. Blood was collected from the posterior vena cava using a heparinized syringe. Liver, muscle (quadriceps), and fat (epididymal and perirenal) were also removed for analysis. Blood samples (1.0 mL for all chemicals) were placed in 12.4 mL glass vials and incubated/ mixed for 3 hrs at 37°C with 400 ppm of chemical (800 ppm for CF_3I) in the vial headspace. Whole tissue samples (1.0 g of liver and muscle, and 0.5 g of fat for all chemicals) were minced and incubated/mixed under the same condition as for blood, except fat was equilibrated for 5-8 hrs. Partition coefficients were also determined at 80 and 400 ppm to show that they were concentration independent.

The chemical concentrations in the headspace were analyzed using a HP19395A headspace sampler (Hewlett-Packard, Avondale, PA) connected to a HP5890A gas chromatograph (GC) (Hewlett-Packard, Palo Alto, CA) equipped with a hydrogen flame ionization detector. Column selection and GC conditions varied for each chemical. CF_3I and $C_6F_{13}I$ a 12' x 1/8" stainless steel 10% SE-30, WHP 80/100 mesh Chromsorb column was used. A DB-17 column was used for C_3F_7I. GC conditions were set with the detector temperature at 250°C for CF_3I and $C_6F_{13}I$ and 300°C for C_3F_7I, injector temperature at 125°C, nitrogen carrier gas flow at 30.0 mL/min, and an oven temperature held constant at 60°C for CF_3I, 80°C for C_3F_7I, and 100°C for $C_6F_{13}I$.

Gas Uptake and Metabolic Constants

Figure 1 illustrates the closed chamber recirculating gas uptake system with a volume of 8.0 L that was used for the estimation of the whole animal metabolic constants (V_{max}, K_m, and/or K_f). The condenser was removed for $C_6F_{13}I$ and C_3F_7I. Three F-344 rats were exposed to each study chemical using a gas uptake system similar to that described by Gargas et al. (1986). Initially, a predetermined concentration of the test chemical was introduced into the system so that the concentration in the chamber atmosphere decreases as the chemical is taken up and metabolized by the rat. Four to five exposure concentrations were performed for 6 hours for each chemical (CF_3I concentrations were 112, 648, 1228, 2727 and 5867 ppm; $C_6F_{13}I$ concentrations were 124, 540, 1043, and 4822 ppm; C_3F_7I concentrations were 245, 1108, 3012, and 5126 ppm). Sodium hydroxide (75-150 g) was used as the CO_2 absorber for CF_3I. Barium hydroxide (75 g) was used as the CO_2 absorber for C_3F_7I and $C_6F_{13}I$. Oxygen concentrations were maintained at (21 +/- 1%) during the exposures. The system flow was maintained at 2.1 L/min with the flow to the sample loop of the GC at 100 mL/min.

The chemical concentrations in the chamber atmosphere were monitored every 5 min for the first 30 min and every 15 min thereafter using an automated gas sampling valve connected to a HP5890A gas chromatograph. Chromatography was performed on a 25m x 0.53 mm Chrompack PoraPLOT Q (Plot Fused Silica) column for CF_3I. The GC was equipped with a hydrogen flame ionization detector with a temperature of 250°C, helium carrier flow at 12.1 mL/min with make-up flow of 14.2 mL/min, injector at 125°C, and an oven temperature held constant at 125°C for CF_3I. Chromatography was performed on a 10% SE-30, WHP 80/100 mesh Chromosorb 12' x 1/8' ss column for $C_6F_{13}I$ and C_3F_7I. The

detector (FID) temperature was 250°C, injector temperature was 125°C, oven temperature was held constant at 100°C for $C_6F_{13}I$ and at 50°C for C_3F_7I, and helium carrier flow was at 30 mL/min.

Model Development -

SIMUSOLV (DOW Chemical Co., Midland, MI), a FORTRAN-based continuous simulation language with optimization capabilities was used on a VAX/VMS 8530 mainframe computer (Digital Equipment Corp., Maynard, MA). Figure 2 shows a general form of a PBPK model. The codes that made up the PBPK models are given in the Appendices. Parameters were optimized by SIMUSOLV which is using the log likelihood function as the criterion and either the generalized reduced gradient method for single parameter optimization or the Nelder-Mead search method for multiple parameters optimization to adjust the values.

Physiological constants for calculating volumes of the compartments are shown in Table 1. Tissue volume and flow constants are scaled to the actual body weight (BW) of the rats under study (fat volume was derived from Anderson et al. [1993]); other constants were according to Linstedt (Physiological Parameters Working Group, ILSI Risk Science Institute, unpublished data). Blood flows are expressed as a percentage of cardiac output that was scaled to body weight to the exponent 0.75. Alveolar ventilation is also scaled to body weight to the exponent 0.75. Cardiac output and alveolar ventilation, based on those described by Gargas et al. (1986) for resting animals, are summarized in Table 1.

Blood/air and tissue/air partition coefficients were obtained as described above. Metabolic constants were determined using the model to obtain a simultaneous fit to the closed chamber gas uptake data. The constants are scaled to BW using the allometric relationship described by Andersen et al. (1987).

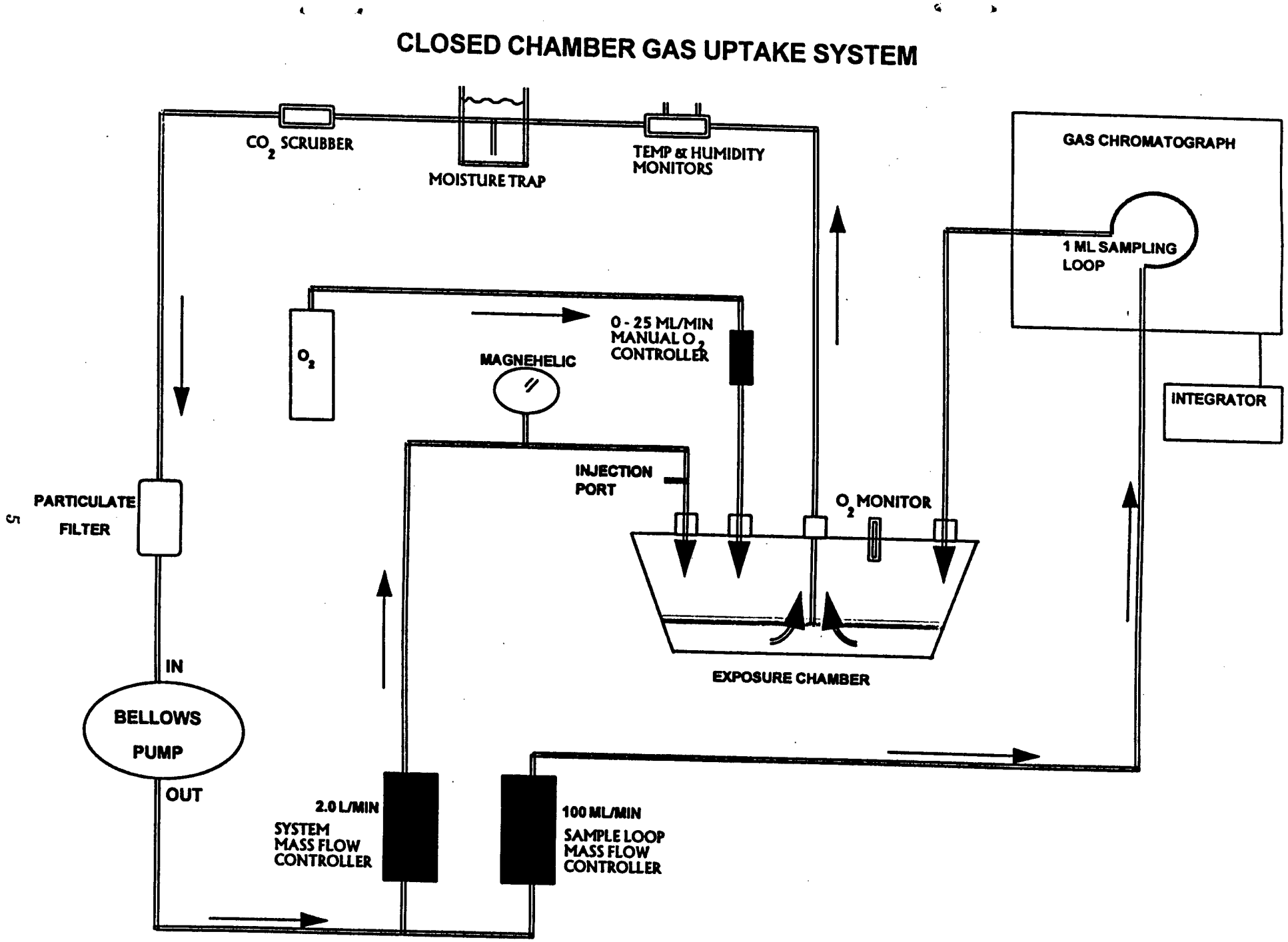


Figure 1. Illustration of Closed Chamber Recirculating Gas Uptake System (FM: flowmeter, MH: magnahelic, inj: injection, temp: temperature, hum: humdity)

UPTAKE2.PPT

TABLE 1. KINETIC CONSTANTS AND PHYSIOLOGICAL PARAMETERS USED IN PBPK MODELING IN RATS

DESCRIPTION	[UNITS] PARAMETERS
Tissue Volumes	**[Fraction of Body Weight: BW]**
Liver	$V_LC = 0.037$
Fat	$V_FC = 0.1*(35*BW+2.1)$
Slowly Perfused	$V_SC = 0.558$
Rapidly Perfused	$V_RC = 0.031$
Flow Rates	**[L/h/kg]**
Alveolar Ventilation	$Q_PC = 14.0$
Cardiac Output	$Q_CC = 14.0$
	[Fraction of Cardiac Output]
Liver	$Q_LC = 0.032$
Fat	$Q_FC = 0.058$
Slowly Perfused	$Q_SC = 0.255$
Rapidly Perfused	$Q_RC = 0.472$

PBPK Model Construction

Figure 2 shows the scheme of the PBPK model, essentially as described by Ramsey and Andersen (1984). Mass transfer differential equations describing each department of the PBPK model for all chemicals are presented below.

For simple, well-stirred compartments in which neither metabolism nor other losses occurred (rapidly and slowly perfused tissues, and fat), the change in the amount of chemical (A_i) over time (t) was described as follows:

$$dA_i/dt = Q_i(CA-CV_i)$$

where subscript $_i$ represents "i-th" compartment; Q_i represents the blood flow through the "i-th" compartment; CA represents the arterial concentration; CV_i represents the venous concentration leaving the "i-th" compartment ($CV_i = C_i/P_i$; where C_i is a concentration in the tissues in the "i-th" compartment and P_i is the tissue/ blood partition coefficient for the "i-th" compartment. $C_i = A_i/V_i$, where V_i represents the volume of the "i-th" compartment).

For the liver compartment, a loss term (RAM) was added to he well-stirred compartment description to account for rate of metabolism ($RAM = V_{max}\ CV_L/(K_m + CV_L) + K_f*CV_L*V_L$; where V_{max} is apparent-maximal velocity rate of metabolism, CV_L is venous concentration leaving the liver, K_m is apparent Michaelis-Menten constant, K_f is the first-order rate of metabolism, and V_L is the volume of the liver):

$$dA_L/dt = Q_L(CA-CV_L)-RAM$$

Units for the above variables are as follows: amounts-mg, concentrations-mg/L, flows-L/h, and rates-mg/h. The actual codes and command files used for computer simulation of the Iodohalogenated compounds are included in the appendices.

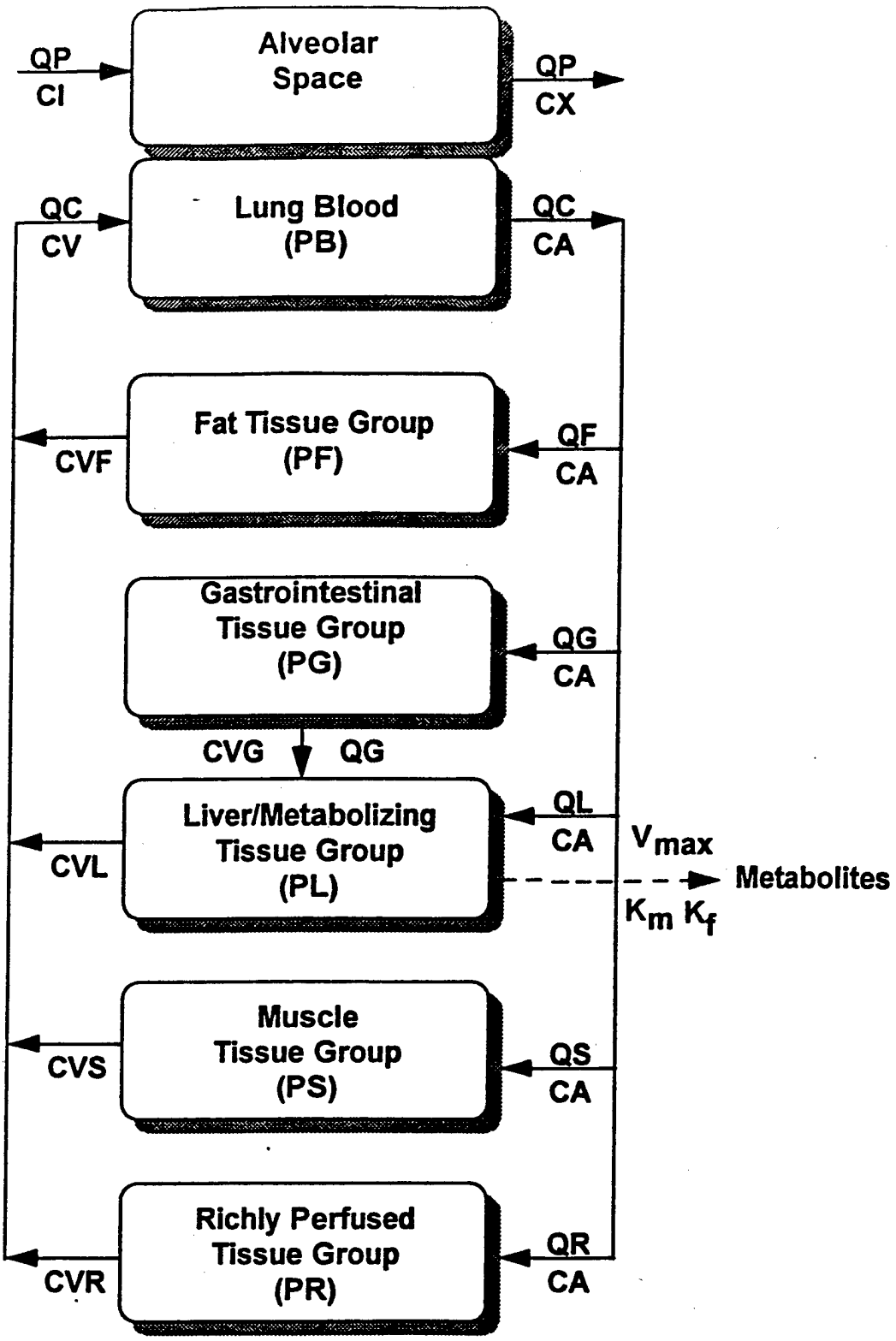


Figure 2. A Scheme of PBPK model used for the computer simulations of Halon 1301 and its proposed replacements disposition and metabolism in rats.

SECTION 3
RESULTS

Partition Coefficients -

Shown in Table 2 are the rat tissue to air partition coefficients determined for CF_3I, $C_6F_{13}I$, and C_3F_7I, which were used in the PBPK model optimization. Due to the extremely low partition coefficient for FC-218, higher amounts of rat tissue were used.

TABLE 2. PARTITION COEFFICIENTS FOR IODOHALOGENATED COMPOUNDS

Partition Coeffients		CF_3I (n = 10)	$C_6F_{13}I$ (n = 5)	C_3F_7I (n = 5)
Blood:air	PB	1.73 ± 0.28	0.94 ± 0.2	0.54 + 0.3
Liver:air	PLA	1.27 ± 0.21	0.90 ± 0.4	0.02 + 0.27
Fat:air	PFA	10.35± 0.82	130.6± 17.9	11.21+ 1.53
Rapidly perfused:air	PRA	1.27 ± 0.21	0.90 ± 0.4	0.02 + 0.27
Slowly perfused:air	PSA	1.32 ± 0.18	1.0 ± 0.2	0.50 + 0.27

Gas Uptake Studies

The inhalation uptake of CF_3I was reported in AL/OE-TR-1994-0068. The rat showed two discernible phases: a rapid equilibration phase that lasted up to 60 min followed by a slow linear uptake phase. Simulation of uptake of CF_3I required some attribution of metabolic capacity by the rats. Attribution of both saturable (V_{maxc}= 0.375, K_m= 0.1) and first order (K_{fc}= 1.6) metabolism and a chamber loss of 2.7% is shown compared to no metabolism with the same chamber loss rate. The upper curve with each set of data represents the no metabolism condition. Attribution of saturable (V_{maxc}= 0.375, K_m= 0.1) metabolism alone and a chamber loss of 4% is shown compared to no metabolism with a chamber loss of 2.7%. Comparing the simulations with metabolism and the simulations without metabolism, virtually overlapping each other. This indicates a lack of discrimination between first order metabolism and chamber loss for CF_3I.

The inhalation uptake of $C_6F_{13}I$ also had two phase: a two hour equilibration phase followed by a slow linear uptake phase. The two hour equilibration phase is caused by the chemcial's absorption to the barium hydroxide. Simulation of uptake of $C_6F_{13}I$ required some attribution of metabolic capacity by the rats. First order (K_{fc}= 8.61) metabolism with a chamber loss rates of 7.25% for the first two hours and 2.23% for the last four hours is shown compared to no metabolism with the same chamber loss rates (Figure 3). Simulation of C_3F_7I required some attribution of metabolic capacity by the rats. First order (K_{fc}=142.21) metabolism with a chamber loss rate of 1.9% per hr (Figure 4).

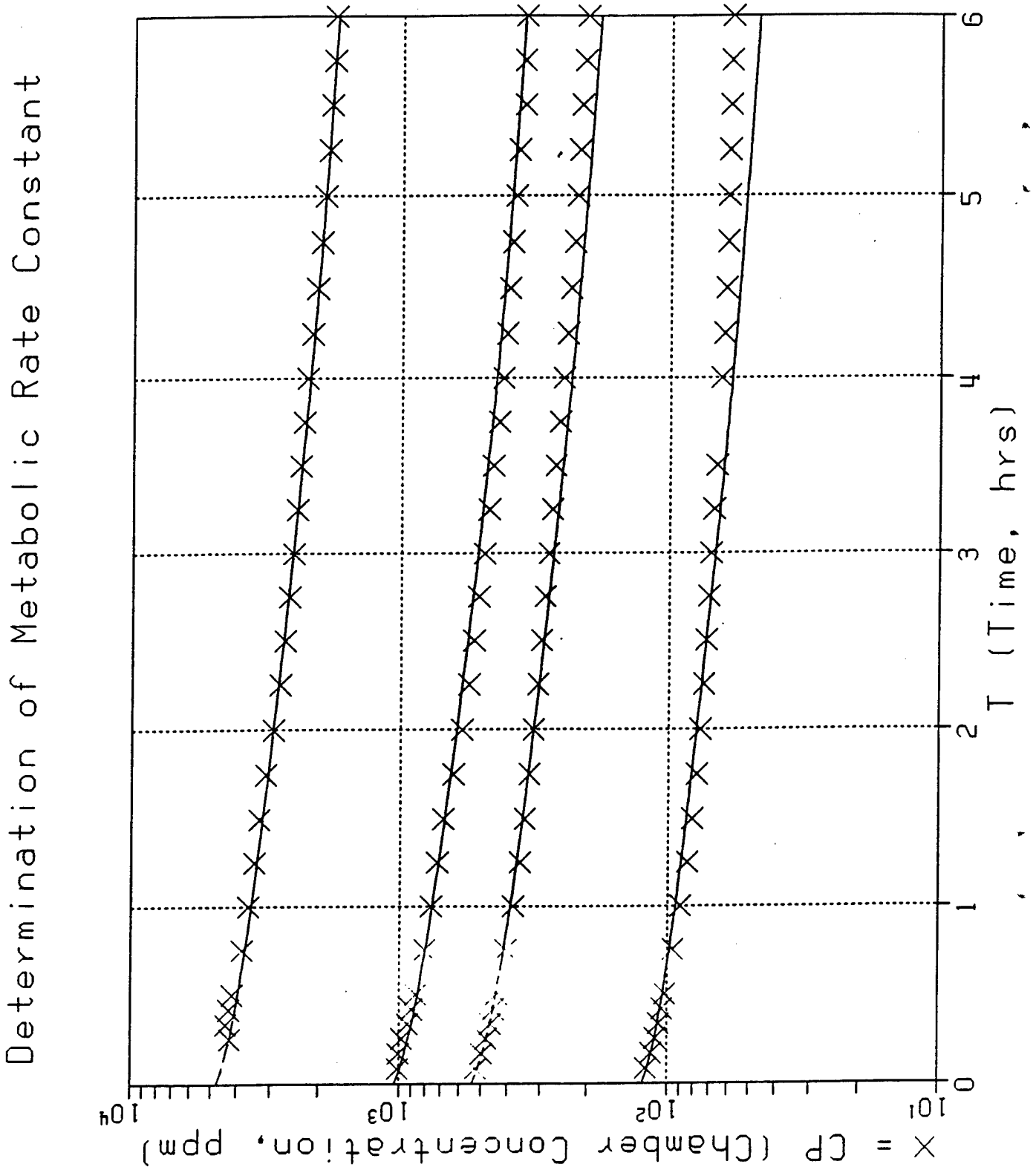
The constants and rates used for each of the preceding simulations are summarized in Table 3.

TABLE 3. SUMMARY OF METABOLIC CONSTANTS AND CHAMBER LOSS RATES USED IN SIMULATING UPTAKE OF IODOHALOGENATED COMPOUNDS BY RATS

FIGURE	CHEMICAL	V_{maxc} mg/h/kg	K_m mg/L	K_{fc} 1/h/kg	CHAMBER LOSS / h
*	CF_3I	0.375	0.1	1.6	2.7 %
		0.0	10000	0.0	2.7 %
*	CF_3I	0.375	0.1	0.0	4.0 %
		0.0	10000	0.0	2.7 %
*	CF_3I	0.375	0.1	1.6	2.7 %
		0.375	0.1	0.0	4.0 %
3	$C_6F_{13}I$	0.0	10000	8.61	7.25 % (0-2 hrs)
		0.0	10000	8.61	2.23 % (2-6 hrs)
4	C_3F_7I	0.0	10000	142.21	1.9%

* Williams, et al.(1994)

Figure 3


Determination of Metabolic Rate Constant
X = CP (Chamber Concentration, ppm)
10^1
10^2
10^3
10^4
0
1
2
3
4
5
6
T (Time, hrs)

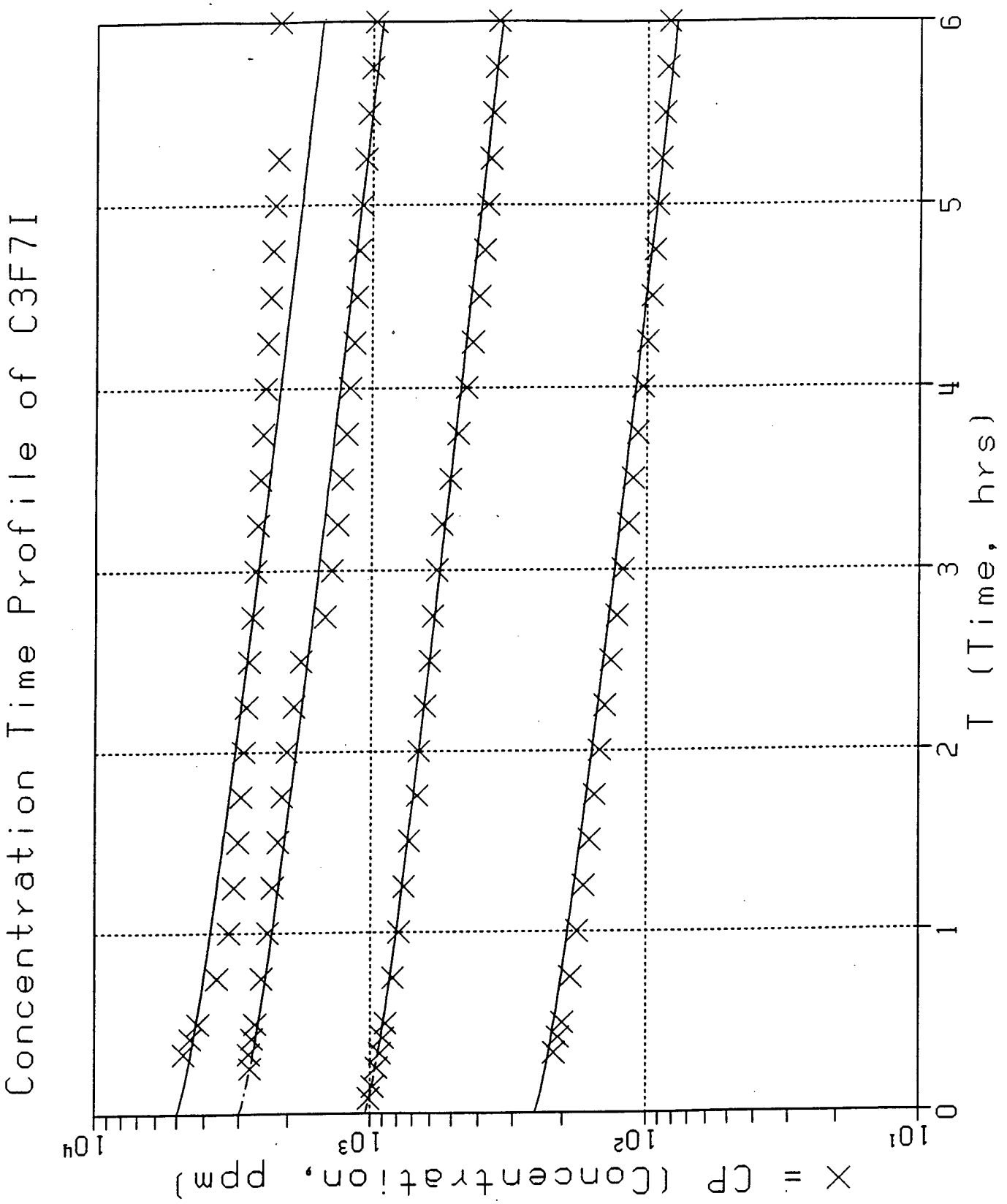

Concentration Time Profile of C3F7I
X = CP (Concentration, ppm)
T (Time, hrs)
10¹
10²
10³
10⁴
0
1
2
3
4
5
6

Figure 4

SECTION 4
DISCUSSION

This simulation approach for analysis of gas uptake data has been shown to distinguish between single and multiple metabolic pathways of several previously studied dihalomethanes and numerous other volatile organic compounds. Simulation of the CF_3I required some attribution of metabolism (saturable and first order) by the rats beyond losses to the system. Another indication that the chemical CF_3I was disappearing beyond that taken up by the chamber is demonstrated by the chromatograms of the chamber air. As gas uptake experiments progressed, a second peak appeared and increased in size. This could represent a metabolite resulting from the metabolism of the chemical by the rats or could represent a product resulting from spontaneous breakdown of CF_3I in the chamber. The product appeared only when live rats were in the chamber with the presence of the parent chemical. However, further experiments would be necessary to determine the identity and origin of the second chromatographic peak.

It was discovered in the loss runs that $C_6F_{13}I$ absorbs to the sodium hydroxide and the skin and fur of the rat. Barium hydroxide was used as the CO_2 absorber because it had a lower chamber loss rate. Since the chemical absorbs to the barium hydroxide and the animal, there is a two hour equilibration phase. Thus, the loss of chemical to the system is best explained using two chamber loss rates: 7.25% for the first two hours, and 2.23% for the last four hours. Simulation of $C_6F_{13}I$ required some attribution of metabolism (first order) by the rat beyond the losses to the system. The K_f was 8.61 l/h/kg. Another indication that the chemical was being metabolized was that the rats were very lethargic at the higher concentration. Thus, it is apparent that $C_6F_{13}I$ has an anesthetic effect on the rats.

C_3F_7I also absorbed to sodium hydroxide, and barium hydroxide was used because of the lower chamber loss rate of 1.9% per hour. The simulation of C_3F_7I required some attribution of metabolism (first order) by the rat beyond the losses to the system. The K_f was 142.21 l/h/kg

SECTION 5
CONCLUSION

1. The PBPK model adequately describes the uptake of CF_3I, $C_6F_{13}I$, and C_3F_7I from the chamber atmosphere during the exposure experiments.

2. CF_3I has low solubility (partitioning) in blood and tissues and had minimal, if any, enzymatic metabolism in rats.

3. Further experimentation is needed to determine the identity of the second peak in the metabolism of CF_3I.

4. $C_6F_{13}I$ has an anesthetic effect on the rats.

SECTION 6
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